



General

Guideline Title

VA/DoD clinical practice guideline for the management of major depressive disorder.

Bibliographic Source(s)

Management of Major Depressive Disorder Working Group. VA/DoD clinical practice guideline for the management of major depressive disorder. Washington (DC): Department of Veterans Affairs, Department of Defense; 2016 Apr. 173 p. [200 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Management of MDD Working Group. VA/DoD clinical practice guideline for management of major depressive disorder (MDD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009 May. 203 p.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the Department of Veterans Affairs and the Department of Defense (VA/DoD) and the National Guideline Clearinghouse (NGC): The recommendations for the management of major depressive disorder (MDD) are organized onto 5 sections and an algorithm. The following recommendations are organized into sections reflecting both the typical clinical approach to patients as well as grouped according to the severity of the major depressive disorder. The first four sections (Identification, Assessment and Triage, Treatment Setting, and Management) represent the core activities and decisions involved in caring for an individual with MDD. The last section (Other Treatment Considerations) addresses specific populations, complementary alternatives, and secondary treatment options. See the [original guideline document](#) for the algorithm and evidence tables associated with selected recommendations, including strength of recommendation, recommendation category, and supporting evidence citations.

The strength of recommendation grading (Strong For, Weak For, Strong Against, Weak Against) and recommendation categories (Reviewed, Not reviewed, New-added, New-replaced, Not changed, Amended, Deleted) are defined at the end of the "Major Recommendations" field.

Identification

The Work Group recommends that all patients not currently receiving treatment for depression be screened for depression using the Patient Health Questionnaire-2 (PHQ-2) (Strong For; Not Reviewed, Amended)

Assessment and Triage

For patients with suspected depression, the Work Group recommends an assessment for acute safety risks (e.g., harm to self or others, psychotic features) during the initial assessment and periodically thereafter as needed. (Strong For; Not Reviewed, Amended)

For patients with suspected depression, the Work Group recommends an appropriate diagnostic evaluation that includes a determination of functional status, medical history, past treatment history, and relevant family history. (Strong For; Not Reviewed, Amended)

For patients with a diagnosis of MDD, the Work Group suggests using the PHQ-9 as a quantitative measure of depression severity in the initial treatment planning and to monitor treatment progress (see Recommendation 14 below). (Weak For; Not Reviewed, Amended)

Treatment Setting

The Work Group recommends that patients with complex MDD (severe, chronic or recurrent) be offered specialty care by providers with mental health expertise in order to ensure better outcomes and effective delivery of evidence-based treatment strategies. (Strong For; Reviewed, New-replaced)

The Work Group recommends the use of the collaborative care model for the treatment of MDD within a primary care setting. (Strong For; Reviewed, New-replaced)

Management

Treatment for Uncomplicated Mild to Moderate MDD

The Work Group recommends that treatment planning include patient education about the condition and treatment options, including risks and benefits. The individualized treatment plan should be developed using shared decision-making principles, and should define the provider, patient, and support network's roles. (Strong For; Not Reviewed, Amended)

As first-line treatment for uncomplicated mild to moderate MDD (see Recommendation 17 below for complex cases), the Work Group recommends offering one of the following treatments based on patient preference, safety/side effect profile, history of prior response to a specific medication, family history of response to a medication, concurrent medical illnesses, concurrently prescribed medications, cost of medication and provider training/competence:

Evidence-based psychotherapy:

- Acceptance and commitment therapy (ACT)
- Behavioral therapy/behavioral activation (BT/BA)
- Cognitive behavioral therapy (CBT)
- Interpersonal therapy (IPT)
- Mindfulness-based cognitive therapy (MBCT)
- Problem-solving therapy (PST)

Evidence-based pharmacotherapy:

- Selective serotonin reuptake inhibitor (except fluvoxamine) (SSRIs)
- Serotonin-norepinephrine reuptake inhibitor (SNRIs)
- Mirtazapine
- Bupropion

The evidence does not support recommending a specific evidence-based psychotherapy or pharmacotherapy over another.

(Strong For; Reviewed, New-replaced)

In patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy (maximized) after a minimum of four to six weeks of treatment, the Work Group recommends

switching to another monotherapy (medication or psychotherapy) or augmenting with a second medication or psychotherapy. (Strong For; Reviewed, New-replaced)

For patients who select psychotherapy as a treatment option, the Work Group suggests offering individual or group format based on patient preference. (Weak For; Reviewed, New-replaced)

For patients with mild to moderate MDD, the Work Group recommends offering computer-based cognitive behavioral therapy (CCBT) either as an adjunctive intervention or, based on patient preference, as a first-line treatment. (Strong For; Reviewed, Amended)

For patients with mild to moderate MDD who decline pharmacotherapy and who decline or cannot access first-line evidence-based psychotherapies, the Work Group suggests offering non-directive supportive therapy or short-term psychodynamic psychotherapy. (Weak For; Reviewed, New-replaced)

Treatment of Severe, Chronic or Recurrent MDD (Complex)

The Work Group suggests offering a combination of pharmacotherapy and evidence-based psychotherapy for the treatment of patients with MDD during a new episode of care when the MDD is characterized as:

- Severe (i.e., PHQ-9 >20)

- Chronic (duration greater than two years)

- Recurrent (with three or more episodes)

(Weak For; Reviewed, New-replaced)

Monitoring (All Severities and Complexities of MDD)

After initiation of therapy or a change in treatment, the Work Group recommends monitoring patients at least monthly until the patient achieves remission. At minimum, assessments should include a measure of symptoms, adherence to medication and psychotherapy, and emergence of adverse effects. (Strong For; Reviewed, Amended)

Continuation and Maintenance Treatments (All Severities and Complexities of MDD)

In patients with MDD who achieve remission with antidepressant medication, the Work Group recommends continuation of antidepressants at the therapeutic dose for at least six months to decrease risk of relapse. (Strong For; Reviewed, New-replaced)

In patients at high risk for recurrent depressive episodes (see Discussion sections in the original guideline document) and who are treated with pharmacotherapy, the Work Group recommends offering maintenance pharmacotherapy for at least 12 months and possibly indefinitely. (Strong For; Reviewed, New-replaced)

For patients at high risk for relapse (e.g., two or more prior episodes, unstable remission status), the Work Group recommends offering a course of CBT, IPT or MBCT during the continuation phase of treatment (after remission is achieved) to reduce the risk of subsequent relapse/recurrence.

- The evidence does not support recommending a specific evidence-based psychotherapy over another.

(Strong For; Reviewed, Amended)

Other Treatment Considerations

Recommendations for Specific Populations with Mild or Moderate MDD

For initiation of treatment in pregnant or breastfeeding women with mild to moderate MDD, the Work Group recommends offering an evidence-based psychotherapy (i.e., ACT, BA/BT, CBT, IPT, MBCT, PST) as a first-line treatment.

- The evidence does not support recommending a specific evidence-based psychotherapy over another.

- In pregnant patients with a history of MDD prior to pregnancy who responded to antidepressant medications, and are currently stable on pharmacotherapy, weigh risk/benefit balance to both mother and fetus in treatment decisions.

(Strong For; Reviewed, New-replaced)

For older adults (≥ 65 years) with mild to moderate MDD, the Work Group recommends offering an evidence-based psychotherapy (i.e., ACT, BT/BA, CBT, IPT, MBCT, PST) as a first-line treatment. Patient preference and the additional safety risks of pharmacotherapy should be considered when making this decision.

The evidence does not support recommending a specific evidence-based psychotherapy over another.

(Strong For; Reviewed, New-replaced)

In patients with mild to moderate MDD and significant relationship distress, the Work Group suggests offering couples-focused therapy, either as monotherapy or in combination with pharmacotherapy. (Weak For; Reviewed, New-replaced)

The Work Group suggests offering light therapy for adult patients with mild to moderate MDD with a seasonal pattern (formerly seasonal affective disorder [SAD]). (Weak For; Reviewed, Amended)

Other Considerations for the Treatment of Severe, Chronic or Recurrent MDD (Complex)

For patients with treatment-resistant MDD who had at least two adequate pharmacotherapy trials, the Work Group recommends offering monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs) along with patient education about safety and side effect profiles of these medications. (Strong For; Reviewed, New-replaced)

Given the limited information on ketamine's safety and duration of effect, the Work Group recommends against the use of ketamine to treat MDD outside of a research setting. (Strong Against; Reviewed, New-added)

The Work Group recommends offering electroconvulsive therapy (ECT) with or without psychotherapy in patients with severe MDD and any of the following conditions:

- Catatonia

- Psychotic depression

- Severe suicidality

- A history of a good response to ECT

- Need for rapid, definitive treatment response on either medical or psychiatric grounds

- Risks of other treatments outweigh the risks of ECT (i.e., co-occurring medical conditions make ECT the safest treatment alternative)

- A history of a poor response to multiple antidepressants

- Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety)

- Patient preference

- Pregnancy

(Strong For; Reviewed, Amended)

The Work Group suggests offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant MDD. (Weak For; Reviewed, New-added)

The Work Group recommends against offering vagus nerve stimulation (VNS) for patients with MDD, including patients with severe treatment-resistant depression outside of a research setting. (Strong Against; Reviewed, Amended)

The Work Group recommends against offering deep brain stimulation (DBS) for patients with MDD outside of a research setting. (Strong Against; Reviewed, New-added)

Self-help and Complementary and Alternative Treatments

For patients with MDD, there is insufficient evidence to recommend for or against acupuncture either as monotherapy or as an adjunctive treatment to pharmacotherapy. (Not Applicable; Reviewed, New-replaced)

For patients with MDD, the Work Group suggests offering patient education on the benefits of exercise as an adjunct to other evidence-based treatments for depression or as monotherapy when patients are unwilling or unable to engage in first-line evidence-based psychotherapy or

pharmacotherapy. (Weak For; Reviewed, New-replaced)

For patients with MDD, there is insufficient evidence to recommend for or against yoga, tai chi, or qi gong either as monotherapy or as an adjunctive treatment to pharmacotherapy. (Not Applicable; Reviewed, New-added)

For patients with mild MDD who are not pregnant or breastfeeding and who prefer herbal treatments to first-line psychotherapy or pharmacotherapy, the Work Group suggests standardized extract of St. John's wort (SJW) as a medication monotherapy. (Weak For; Reviewed, Amended)

For patients with MDD, the Work Group suggests against using omega-3 fatty acids or vitamin D for treatment. (Weak Against; Reviewed, New-added)

For patients with mild MDD, the Work Group suggests patient education about the benefits of bibliotherapy based on cognitive-behavioral principles as adjunctive treatment or an alternative to pharmacotherapy or psychotherapy based on patient preference. (Weak For; Reviewed, New-replaced)

Definitions

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

Strong For (or "The Work Group recommends offering this option ...")

Weak For (or "The Work Group suggests offering this option ...")

Weak Against (or "The Work Group suggests not offering this option ...")

Strong Against (or "The Work Group recommends against offering this option ...")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Recommendation Categories and Definitions

For use in the 2016 MDD Clinical Practice Guideline (CPG), a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Care Excellence (NICE). These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated.

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made

Evidence Reviewed* Not reviewed	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
	Recommendation Category*	Definition*
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) and Garcia et al. (2014).

Abbreviation: CPG: clinical practice guideline

Clinical Algorithm(s)

An algorithm for identification, assessment and triage, and management of major depressive disorder is provided in the original guideline document.

Scope

Disease/Condition(s)

Major depressive disorder (MDD)

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Psychiatry

Psychology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

Guideline Objective(s)

- To assist providers in managing patients with major depressive disorder (MDD)
- To offer best practice advice on the care of adults who have a diagnosis of MDD
- To recommend optimal assessment and diagnosis for MDD
- To recommend best practices for treatment interventions (pharmacotherapy, psychotherapies, and somatic therapies) in patients with MDD
- To address indications for consultation and referral to specialty care

Target Population

Adults 18 years or older with major depressive disorder (MDD) being treated in any Department of Veterans Affairs/Department of Defense (VA/DoD) clinical setting, including those newly diagnosed, those receiving ongoing treatment and those with chronic depression

Note: This Clinical Practice Guideline (CPG) does not provide recommendations for the management of MDD in children or adolescents, or for the management of co-occurring disorders. The CPG also does not consider the management of unspecified depressive disorder, or complicated bereavement or the range of other depressive disorders identified in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*): disruptive mood dysregulation disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder or unspecified depressive disorder (depression not otherwise specified). The principles in this document should be strongly considered when treating these other depressive disorders and in particular, unspecified depressive disorders.

Interventions and Practices Considered

Screening/Diagnosis/Evaluation

Screening patients using the Patient Health Questionnaire-2 (PHQ-2)

Assessment of patient at risk of harm to self or others

Diagnostic evaluation including functional status, medical history, treatment history, and family history

Using the PHQ-9 as a quantitative measure of depression severity

Management/Treatment

Offering specialty care by providers with mental health expertise

Use of collaborative care model within primary care setting

Treatment of uncomplicated mild to moderate major depressive disorder (MDD)

Treatment planning including patient education

Evidence-based psychotherapy in individual or group format: acceptance and commitment therapy (ACT); behavioral therapy/behavioral activation (BT/BA); cognitive behavioral therapy (CBT), including computer-based cognitive behavioral therapy (CCBT); interpersonal therapy (IPT); mindfulness-based cognitive therapy (MBCT); problem-solving therapy (PST)

Evidence-based pharmacotherapy: selective serotonin reuptake inhibitors (except fluvoxamine) (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), mirtazapine, bupropion

Non-directive supportive therapy or short-term psychodynamic psychotherapy

Treatment of severe, chronic, or recurrent MDD (complex): combination of pharmacotherapy and evidence-based psychotherapy

Monitoring of patient symptoms, adherence to medication and psychotherapy, adverse effects

Continuation and maintenance treatments

Treatment of special populations (pregnant and breastfeeding women, the elderly, couples, people with MDD with a seasonal pattern)

Other treatment considerations for severe, chronic, or recurrent MDD (complex)

- Use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs)
- Ketamine (not recommended)
- Electroconvulsive therapy (ECT)
- Repetitive transcranial magnetic stimulation (rTMS)
- Vagus nerve stimulation (VNS) (not recommended)
- Deep brain stimulation (DBS) (not recommended)

Self-help and complementary and alternative treatments

- Acupuncture (no recommendation for or against)
- Exercise
- Yoga, tai chi, or qi gong (no recommendation for or against)
- St. John's wort
- Omega-3 fatty acids or vitamin D (not recommended)
- Bibliotherapy

Major Outcomes Considered

- Sensitivity and specificity of screening tools
- Improvement in quality of life (social and occupational functioning)
- Improvement of symptoms
- Remission rate
- Relapse and recurrence rate
- Medication adherence and dropout
- Improvement of retention (keeping patients engaged in programs)
- Improvement in co-occurring conditions
- Adverse events (i.e., behavioral: agitation, anxiety, irritability, hostility, impulsivity; mortality/suicide; sexual side effects; weight gain; cardiovascular symptoms; worsening of depression; fatigue/sleepiness; insomnia; nausea, vomiting, diarrhea; neurological symptoms; and urological symptoms)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Developing the Scope and Key Questions

The Clinical Practice Guideline (CPG) Champions, along with the Work Group, were tasked with identifying key evidence questions to guide the systematic review of the literature on major depressive disorder (MDD). These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the Department of Veterans Affairs and Department of Defense (VA and DoD) populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare

Research and Quality (AHRQ). Table A-1 in the original guideline document provides a brief overview of the PICOTS typology.

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 in the original guideline document contains the final set of key questions used to guide the systematic review for this CPG.

Conducting the Systematic Review

Extensive literature searches identified 4,601 citations potentially addressing the key questions of interest to this evidence review. Of those, 2,470 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, not a full-length article). Overall, 2,131 abstracts were reviewed with 1,089 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a key question of interest to this review, did not enroll a population of interest, or was published prior to January 2006. A total of 1,042 full-length articles were reviewed. Of those, 520 were excluded at a first pass review for the following reasons: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for a clinical study or systematic review, not meeting inclusion criteria for any key question, or being a duplicate. A table listing all studies excluded at the full-article level is included as a separate file to this report. A total of 522 full-length articles were thought to address one or more key questions. However, upon further review, 398 additional studies were excluded. Reasons for their exclusion are presented in Figure A-1 of the original guideline document. Overall, 124 studies addressed one or more of the key questions and were considered as evidence in this review. Table A-2 in the original guideline document indicates the number of studies that addressed each of the questions.

Criteria for Study Inclusion/Exclusion

General Criteria

Systematic reviews published on or after January 1, 2008 and individual clinical studies published on or after January 1, 2006. Including previous systematic reviews published on or after 2008 will ensure that the reviews include individual studies within the date range for this report.

Studies must be published in English.

Publication must be a full-length clinical study, systematic review, or meta-analysis; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence.

Study must have enrolled a patient population in which at least 80% of patients had MDD. Studies enrolling more than 20% of patients with one or more of the following disorders will be excluded: mild depression, dysthymia, psychotic depression, or bipolar disorder.

Studies must have enrolled adults 18 years or older. In studies that mix adults and children, at least 80% of the enrolled patients had to have been 18 years or older.

Treatment Studies

Study must have evaluated a pharmacological or non-pharmacological treatment of interest to this review.

Study must have been a prospective randomized controlled trial (RCT) with an independent control group.

Crossover trials considered only if data from the first treatment period were reported separately.

Study must have enrolled ≥ 10 patients per treatment arm.

The study must report data on at least one of the included outcomes.

Study must have followed patients for 6 to 12 weeks.

All subjective outcomes (e.g., depressive symptoms, quality of life) must have been measured using a validated instrument.

Literature Search Strategy

ECRI Institute information specialists searched the following databases for relevant information:

Bibliographic Databases

Cochrane Library 2006 through January 2015 (Wiley)

EMBASE 2006 through April 2015 (Elsevier)

Health Technology Assessment Database (HTA) 2006 through January 2015 (Wiley)

Medline 2006 through April 2015 (Elsevier)

PsycINFO 2006 through April 2015 (OVIDSP)

PubMed (In-process, Publisher, and PubMed-Not-Medline records), and Agency for Healthcare Research and Quality (AHRQ) 2006 through April 2015 (National Library of Medicine [NLM])

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms. See the tables in Appendix A of the original guideline document for search strategies.

Gray Literature Resources

Agency for Healthcare Research and Quality (AHRQ) (2006 through February 2015 (AHRQ))

Number of Source Documents

Overall, 124 studies addressed one or more of the key questions and were considered as evidence in the review. See Figure A-1 in the original guideline document for a study flow diagram.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence and Definitions*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

*Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J. & the GRADE Working Group. (2008). GRADE; An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 336, 924-926.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Abstraction and Data Management

For each study included in the review, the following study level details were abstracted: country, purpose, and quality rating. For previous systematic reviews, the search strategy used, study selection criteria, and overall information about the evidence base, including number of included studies and overall patients enrolled, were reported. For intervention studies and previous systematic reviews, the reviewers also abstracted data about the characteristics of the included patients and treatments being assessed. Finally, for all studies, they abstracted data on the findings for the outcomes of interest for this review.

Assessment of Individual Study Quality (Methodological Risk of Bias of Individual Studies)

Risk-of-bias (or study quality) of individual studies was assessed using the U.S. Preventive Services Task Force (USPSTF) method. Each study was assigned a rating of Good, Fair, or Poor based on sets of criteria that vary depending on study design. Detailed lists of criteria and definitions of Good, Fair, or Poor ratings for different study designs appear in Appendix VII of the [USPSTF procedure manual](#)

Data Synthesis

The evidence review team used a narrative approach to synthesizing the evidence for all the Key Questions. As indicated in the Department of Veterans Affairs/Department of Defense (VA/DoD) *Guidelines for Guidelines* document, the first line of evidence was previous systematic reviews. For questions in which a previous review was available, individual studies that met this review's inclusion criteria were used to supplement or update the previous review. For questions where multiple systematic reviews with similar arrays of included individual studies were available, the reviewers chose the most comprehensive (in terms of the number of high-quality cited studies) and/or recent systematic review for the evidence synthesis in order to avoid multiple ratings of a similar evidence base. Additional systematic reviews not contributing to the overall grading of evidence may be included in narrative summaries of the findings, particularly if they contained a small number of unique, but high-quality, individual studies. For questions for which no previous review was available, the evidence review team summarized the overall findings for the outcomes of interest of individual studies that met inclusion criteria and addressed a key question.

Assessing the Overall Quality of the Body of Evidence for an Outcome

The overall quality of the body of evidence supporting the findings for the outcomes of interest in this report was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. Given time and resources, other factors such as publication bias may also be considered. For more information on the GRADE system go to the [GRADE Working Group Web site](#)

The GRADE system rates the overall quality of the evidence as high, moderate, low, and very low (see the "Rating Scheme for the Strength of the Evidence" field). For instance, a body of evidence that consists of randomized controlled trials (RCTs) automatically starts with a rating of high quality. This rating can be downgraded if some of the RCTs have serious flaws such as lack of blinding of outcome assessors, not reporting concealment of allocation, or high dropout rate. Similarly, the quality can be downgraded or further downgraded if inconsistencies of findings are present or if there is a lack of precision surrounding an outcome's effect size.

Assessing Applicability

When describing the evidence base addressing a Key Question, the reviewers discussed aspects of the included studies, such as inclusion/exclusion criteria, characteristics of included patients, and characteristics of the treatments being assessed, that may make the overall findings of the studies more or less applicable to the population, treatments, or outcomes of interest to the review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The current document is an update to the 2009 Major Depressive Disorder Clinical Practice Guideline (MDD CPG). The methodology used in developing the 2016 CPG follows the *Guideline for Guidelines*, an internal document of the Department of Veterans Affairs and Department of Defense (VA and DoD) Evidence-Based Practice Working Group (EBPWG) (see the "Availability of Companion Documents" field). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA/DoD, known as the Work Group, and ultimately, the development and submission of an updated MDD CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations, and writing and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions and the Work Group for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management of patients with MDD. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level of quality of the evidence. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence-Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified two clinical leaders as Champions for the 2016 MDD CPG.

The Lewin Team (Team), including The Lewin Group, Duty First Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and to conduct the evidence review. The Team held the first conference call in November 2014, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence-Based Practice, the DoD Champion and the initial VA Champion. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management of MDD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of MDD from which Work Group members were recruited. The specialties and clinical areas of interest included: psychiatry, psychology, nursing, pharmacy, social work, family medicine, internal medicine, emergency medicine, and mental and behavioral healthcare. The guideline development process for the 2016 MDD CPG update consisted of the following steps:

- Formulating evidence questions (key questions)
- Conducting the systematic review
- Convening a face-to-face meeting with the CPG Champions and Work Group members
- Reviewing former recommendations not included in the systematic review and without an updated literature review
- Drafting and submitting a final MDD CPG to the VA/DoD EBPWG

Appendix A in the original guideline document provides a detailed description of each of these tasks.

The Face-to-Face Meeting

In consultation with the COR, the Champions, the Work Group, and the Lewin Team convened a three and

a half day face-to-face meeting of the CPG Champions and Work Group members on June 2-5, 2015. These experts were gathered to develop and draft the clinical recommendations for an update to the 2009 MDD CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to categorize recommendations from the 2009 MDD CPG. The members also developed new clinical practice recommendations not presented in the 2009 MDD CPG, based on the 2015 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) and U. S. Preventive Services Task Force (USPSTF) methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group members also revised the 2009 MDD CPG algorithms to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2009, as necessary, to update the algorithms.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:

- Balance of desirable and undesirable outcomes

- Confidence in the quality of the evidence

- Values and preferences

- Other implications, as appropriate:

 - Resource Use

 - Equity

 - Acceptability

 - Feasibility

 - Subgroup considerations

The framework in Table A-3 in the original guideline document ("Evidence to Recommendations Framework") was used by the Work Group to guide discussions on each domain.

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework, which combines the four domains. GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low. In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction

- Relative strength (Strong or Weak)

- Direction (For or Against)

Reconciling 2009 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous recommendations based on new evidence or as scheduled according to time-based expirations. For example, the USPSTF has a process for periodically refining or otherwise updating its recommendations pertaining to preventive services. Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed, or revised within the past five years.

The MDD CPG Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the key questions. In addition to those new and updated recommendations, the CPG Work Group considered the current applicability and relevance of the remaining recommendations that were made in the previous 2009 MDD CPG. While these remaining 2009 recommendations were reviewed by the group, the literature supporting these recommendations was not reviewed as part of a systematic literature search. Therefore, the determination of carrying forward or modifying these prior recommendations was based on expert opinion as well as on the evidence review from the previous version of the guideline. In order to be fully transparent, Appendix F in the original guideline document displays all the recommendations from the 2009 MDD CPG and the information regarding how 2009 recommendations were incorporated into the 2016 MDD CPG, including the recommendation category and the 2016 recommendation to which it corresponds, if applicable.

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE, UK). These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated. In brief, the categories took into account whether or not the evidence that related to a recommendation was reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current patient care environment and within the scope of the CPG. Additional information regarding these categories and their definitions can be found in Appendix A of the original guideline document. The categories for the recommendations included in the 2016 version of the guideline are noted in the Recommendations (see the "Major Recommendations" field). The categories for the recommendations from the 2009 MDD CPG are noted in Appendix F of the original guideline document.

The CPG Work Group recognized the need to accommodate the transition in evidence rating systems from the 2009 MDD CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system) the CPG Work Group converted the USPSTF strengths of evidence accompanying the carryover recommendations from the 2009 guideline to the GRADE system. As such, the CPG Work Group considered the strength of the evidence cited for each recommendation in the 2009 MDD CPG as well as both the harms and benefits of each intervention, the patients' values and preferences, and other implications, where possible and relevant. The CPG Work Group referred to the available evidence as summarized in the body of the 2009 MDD CPG and did not re-assess the evidence systematically for those recommendations that did not correspond to the current key questions. In some instances, peer-reviewed literature published since the 2009 MDD CPG was selectively considered along with the evidence base used for that CPG. When such newer literature was considered when converting the strength of the recommendation from the USPSTF to GRADE system, it is noted and cited in the discussion that follows the corresponding recommendation, as well as in Appendix E of the original guideline document.

The CPG Work Group recognizes that, while there are sometimes practical reasons for incorporating findings from a previous systematic review, previous recommendations, or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and, therefore, may introduce bias. Another example of a difference between the previous guideline and the current one is that the prior guideline process included a consideration of patients' values and preferences less consistently or systematically, so older recommendations may be less patient-centered.

Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update

discussion sections from the 2009 MDD CPG to support the amended "carried forward" recommendations. The Work Group also considered tables, appendices, and other sections from the 2009 MDD CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

Rating Scheme for the Strength of the Recommendations

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

Strong For (or "The Work Group recommends offering this option ...")

Weak For (or "The Work Group suggests offering this option ...")

Weak Against (or "The Work Group suggests not offering this option ...")

Strong Against (or "The Work Group recommends against offering this option ...")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Recommendation Categories and Definitions

For use in the 2016 major depressive disorder (MDD) Clinical Practice Guideline (CPG), a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Care Excellence (NICE). These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated.

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed

Evidence Reviewed*	Recommendation Category*	Definition*
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*Adapted from the NICE guideline manual (2012) and Garcia et al. (2014).

Abbreviation: CPG: clinical practice guideline

See Appendix A in the original guideline document for further details on categorization.

Cost Analysis

A published cost analysis was reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

After developing the initial draft of the updated Clinical Practice Guideline (CPG), an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Major Depressive Disorder were posted on a wiki Web site for a period of 14 to 20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in the "Peer Review Process" section in the original guideline document. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the Evidence Based Practice Work Group (EBPWG) for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The final 2016 MDD CPG was submitted to the EBPWG in April 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Table A-2 in the original guideline documents indicates the number and type of studies that addressed each of the questions. The evidence base consists primarily of systematic reviews and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improved assessment and management of major depressive disorder (MDD) in adults

Refer to the "Discussion" sections following each recommendation in the original guideline document for information on the balance between benefits and harms for specific recommendations.

Potential Harms

- Discontinuation of antidepressant therapy should be done with a slow taper since withdrawal done too rapidly may result in adverse withdrawal symptoms or return of the original depressive symptoms. Tapering should be guided by the elimination half-life of the medication and by close monitoring of the depressive symptoms.
- The benefits of repetitive transcranial magnetic stimulation (rTMS) outweigh the minimal risks and side effects. The most common adverse events are irritation at the stimulation site and headache.
- Adverse effects of St. John's wort (SJW) include gastrointestinal upset, mild sedation, restlessness, and increased risk of photosensitivity at higher doses. Providers need to be mindful of potential herb-drug interactions of SJW, and carefully review patient's drug profile before prescribing. SJW induces the cytochrome P450 3A4 enzyme, thereby posing a high risk of drug interactions. For example, SJW can decrease the effectiveness of contraceptives, tricyclic antidepressant drugs, cyclosporine, and antiepileptic drugs.

Refer to Appendix C in the original guideline document for details regarding individual antidepressant agents and their corresponding warnings, precautions, and contraindications. Table C-2 in the original guideline document provides antidepressant adverse event profiles.

Contraindications

Contraindications

- Bupropion is contraindicated in patients with a seizure disorder or history of anorexia nervosa or bulimia and can potentially worsen anxiety.
- Mirtazapine should be avoided in patients for whom weight gain or sedation would be problematic.
- St. John's wort (SJW) should not be used in pregnant or breastfeeding women because of lack of safety data in these populations. Taking SJW in combination with selective serotonin reuptake inhibitors (SSRIs) increases the risk of serotonin syndrome and serotonergic adverse events, and is not recommended. Patients taking clopidogrel should avoid SJW because of an increased risk of bleeding.

Refer to Appendix C for details regarding individual agents and their corresponding warnings, precautions, and contraindications.

Qualifying Statements

Qualifying Statements

- The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.
- This Clinical Practice Guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

- Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.
- These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Implementation of the Guideline

Description of Implementation Strategy

This Clinical Practice Guideline (CPG) and algorithm are designed to be adaptable by individual healthcare providers with consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine the best interventions and timing of care for their patients in order to optimize quality and improve clinical outcomes.

Although this CPG represents practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to the development and dissemination of guidelines.

Implementation Tools

Chart Documentation/Checklists/Forms

Clinical Algorithm

Patient Resources

Pocket Guide/Reference Cards

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents and Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Management of Major Depressive Disorder Working Group. VA/DoD clinical practice guideline for the management of major depressive disorder. Washington (DC): Department of Veterans Affairs, Department of Defense; 2016 Apr. 173 p. [200 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Apr

Guideline Developer(s)

Department of Defense - Federal Government Agency [U.S.]

Department of Veterans Affairs - Federal Government Agency [U.S.]

Veterans Health Administration - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

The Management of Major Depressive Disorder Guideline Working Group

Composition of Group That Authored the Guideline

Working Group Members (Department of Veterans Affairs [VA]): David W. Oslin, MD (*Co-Chair*); Karin Glenn, DNP, RN, PMHNP-BC; Janet L. Henderson, MD, PharmD, FACEP; John R. McQuaid, PhD; Edward P. Post, MD, PhD, FACP; Todd Semla, MS, PharmD, BCPS, FCCP, AGSF; Suzanne Thorne-Odem, DNP, FNP-C; Darlene Trytek, LCSW-R

Additional VA Contributor: Maureen E. Metzger, PhD, MPH

Working Group Members (Department of Defense [DoD]): Maj Lucretia Vaughan, MD (*Co-Chair*); MAJ Rhanda J. Brockington, RN, C MSN, FNP-C; Chris M. Crowe, PhD; Marina Khusid, MD, ND, MS; Timothy J. Lacy, MD; Amy M. Lugo, PharmD, BCPS, FAPhA; Kathy S. Mathis, RN, MS; MAJ Nathalie D. Paolino, DO; James Sall, PhD, FNP-BC; MAJ(P) Sebastian R. Schnellbacher, DO, FAAFP, FAPA; LTC Terri L. Yost, PhD, FNP-BC

Office of Quality, Safety and Value Veterans Health Administration: Eric Rodgers, PhD, FNP, BC; Rene Sutton, BS, HCA

Office of Evidence Based Practice U.S. Army Medical Command: Ernest Degenhardt, COL USA (Ret.), RN, MSN, ANP/FNP, BC; Corinne Devlin, MSN, RN, FNP-BC; James Sall, PhD, FNP-BC

Lewin Group: Clifford Goodman, PhD; Christine Jones, MS, MPH; Noelle Porter, MPH, CPH; Raksha Adhikari, MSPH, CPH; Erika Beam, MS; Anjali Jain, MD

ECRI Institute: Stacey Uhl, MS; Jeff Oristaglio, PhD; Nancy Sullivan, BS; Edmond Baganizi, MPH; Mrin Joshi, MS; Oluwaseun Akinyede, MPH

Sigma Health Consulting, LLC: Frances Murphy, MD, MPH

Duty First Consulting: Anita Ramanathan, BA

Financial Disclosures/Conflicts of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 12 months. Verbal affirmations of no COI were also used as necessary during meetings throughout the guideline development process. The project team was also subject to random Web-based surveillance (e.g., ProPublica).

If a project team member reported a COI (actual or potential), then it was reported to the Office of Evidence Based Practice. It was also discussed with the Major Depressive Disorder Clinical Practice Guideline (MDD CPG) Work Group in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the MDD CPG Work Group determined whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If it was deemed necessary, action was taken by the co-chairs and Office of Evidence Based Practice to mitigate the COI, based on the level and extent of involvement.

Due to COI concerns, two Department of Veterans Affairs (VA) co-chairs were replaced early on in the CPG development process. In order to mitigate the risk of bias while maximizing the contributions of those with expertise in a specific area of MDD treatment, co-chairs asked Work Group members to disclose relevant relationships during related guideline development discussions. After discussion among the Champions, Work Group, and VA/Department of Defense (DoD) Leadership, it was decided that members with potential COIs could contribute to the discussions related to their particular areas of expertise as well as the overarching guideline document in order to ensure differing viewpoints and experiences were adequately represented.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Management of MDD Working Group. VA/DoD clinical practice guideline for management of major depressive disorder (MDD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009 May. 203 p.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [Department of Veterans Affairs Web site](#) .

Availability of Companion Documents

The following are available:

VA/DoD clinical practice guideline for the management of major depressive disorder. Clinician guideline summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2016 Apr. 28 p. Available from the [Department of Veterans Affairs \(VA\) Web site](#) .

VA/DoD clinical practice guideline for the management of major depressive disorder. Pocket card. Washington (DC): Department of Veterans Affairs, Department of Defense; 2016 Apr. 13 p. Available from the [VA Web site](#) .

Guideline for guidelines. Washington (DC): Department of Veterans Affairs; 2013 Apr 10. 26 p. Available from the [VA Web site](#) .

Putting clinical practice guidelines to work in VHA. Washington (DC): Department of Veterans Affairs. 64 p. Available from the [VA Web site](#) .

In addition, the following are available in the appendices of the [original guideline document](#) :

Quick guide to the Patient Health Questionnaire (PHQ)

Information on antidepressant pharmacotherapy (dosing and adverse effects information)

Definitions of major depressive disorder and treatment

Patient Resources

The following is available:

VA/DoD clinical practice guideline for the management of major depressive disorder. Patient guide. Washington (DC): Department of Veterans Affairs, Department of Defense; 2016 Apr. 5 p. Available from the [Department of Veterans Affairs \(VA\) Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on September 9, 1999. The information was verified by the guideline developer on January 10, 2000. This summary was updated by ECRI on February 28, 2001. This summary was updated by ECRI on August 15, 2005, following the U.S. Food and Drug Administration advisory on antidepressant medications. This summary was updated by ECRI on October 3, 2005, following the U.S. Food and Drug Administration advisory on Paxil (paroxetine). This summary was updated by ECRI on December 12, 2005, following the U.S. Food and Drug Administration advisory on Paroxetine HCL - Paxil and generic paroxetine. This summary was updated by ECRI Institute on August 2, 2010. This summary was updated by ECRI Institute on May 20, 2011 following the U.S. Food and Drug Administration advisory on antipsychotic drugs. This summary was updated by ECRI Institute on September 12, 2011 following the U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide). This summary was updated by ECRI Institute on April 16, 2012 following the updated U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide). This summary was updated by ECRI Institute on April 7, 2014 following the U.S. Food and Drug Administration advisory on Methylphenidate ADHD Medications. This summary was updated by ECRI Institute on September 1, 2016. The updated information was not verified by the guideline developer.

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